Tropheryma whipplei in Feces of Patients with Diarrhea in 3 Locations on Different Continents

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We examined fecal specimens of patients with diarrhea from 3 continents for *Tropheryma whipplei* and enteropathogens. *T. whipplei* was most common in South Africa, followed by Singapore and Germany. Its presence was associated with the presence of other pathogens. An independent causative role in diarrhea appears unlikely.

Tropheryma whipplei is the causative agent of Whipple disease (*1*). The organism has also been detected in the feces of healthy or asymptomatic persons (*2*,*3*) and in the feces of patients with diarrhea (*4*–*6*). A causative role in gastroenteritis has been proposed.

To investigate the role of enteric *T. whipplei*, we examined fecal specimens of patients with diarrhea using conventional methods and PCR to detect enteric pathogens and *T. whipplei*. Our aim was to collect epidemiologic evidence regarding a causative role of *T. whipplei* in diarrhea.

The Study

The 3 participating sites were the Molecular Biology Laboratory, AMPATH (Centurion, South Africa); the Department of Pathology and Laboratory Medicine at KK Women's and Children's Hospital (Singapore); and the Institute of Microbiology and Hygiene at the University Hospital Regensburg (Regensburg, Germany). We examined fecal samples from patients with diarrhea that were submitted for microbiological laboratory diagnosis; we used a combination of conventional tests and multiplex PCRs covering the pathogens shown in Table 1, with differences owing to local arrangements (Appendix, https://wwwnc.cdc.gov/EID/article/27/3/20-0182-App1.pdf).

We investigated a total of 590 fecal samples. In South Africa, 97 of 100 targeted samples were usable. In Singapore, 193 of 200 targeted specimens contained sufficient material; of these, 19 were originally submitted for bacterial culture, 77 for rotavirus antigen testing, and 97 for both. In Germany, we tested samples from 300 patients. In South Africa and Singapore, patients were mainly children, both outpatients and inpatients. In Singapore, the total included 13 immunocompromised children with hematologic/oncologic diseases and 1 with a short bowel syndrome. In Germany, all were inpatients and mostly elderly, about one quarter from the hematologic/oncologic ward (Figure).

Overall, 56 patients had positive test results for *T. whipplei* in the feces: 17 (17.5%) in South Africa, 29 (15%) in Singapore, and 10 (3.3%) in Germany. The frequency distribution of the organisms detected is shown in Table 1. In South Africa, *T. whipplei* was the most common fecal organism, followed by *Shigella*, rotavirus, and adenovirus. In Singapore, rotavirus was the most frequently detected organism, followed by norovirus, *T. whipplei*, and *Salmonella*. In Germany, *Clostridioides difficile* was the most frequently detected organism, followed by *T. whipplei* and *Blastocystis hominis*; viruses were not sought in Germany. The frequency of *C. difficile* likely reflects the high proportion of elderly inpatients.

Fecal specimens testing positive for *T. whipplei* averaged 0.91 other pathogens per specimen, in contrast to only 0.46 per specimen in those testing negative for *T. whipplei* ($p = 0.0001$; Table 2). Similarly, of the fecal specimens testing positive for *T. whipplei*, 69.6% contained other pathogens, in contrast to only 34.5% of the specimens testing negative for *T. whipplei* ($p<0.0001$; Appendix Table 1). Thus, specimens con-

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taining *T. whipplei* contained other pathogens about twice as frequently as specimens without *T. whipplei*. In Singapore, 1 specimen contained 4 pathogens: *T. whipplei*, *Blastocystis*, astrovirus, and *Dientamoeba*.

Data on watery consistency and the presence of blood in feces were available for South Africa and Singapore, and microscopy data (e.g., erythrocytes, mucus, yeast cells) were available for South Africa (Appendix Table 2). There was no apparent relationship between these parameters and the presence of *T. whipplei*. Thus, an independent diarrheagenic role of *T. whipplei* was not apparent from these macroscopic and microscopic findings.

An association between the presence of *Campylobacter* and *T. whipplei* (Appendix Table 3) became apparent. Of 534 *T. whipplei*–negative fecal samples, 21 (3.9%) were positive for *Campylobacter* across all sites, whereas 8 (14.3%) of 56 *T. whipplei*–positive samples were positive for *Campylobacter*. This difference was statistically significant (p = 0.0035). In relative terms, specimens carrying *T. whipplei* contained *Campylobacter* 3 times more commonly than those without *T. whipplei*. When looking at the frequency ranking for all pathogens, *Campylobacter* rose from seventh position in *T. whipplei*–negative samples to being the fourth most common enteropathogen in *T. whipplei*–positive samples in South Africa and from fourth to second position in Singapore, whereas the position in Germany remained unchanged (Appendix Table 4).

The mechanisms underlying the *Campylobacter*–*Tropheryma* association remain unclear, but may include similar modes of acquisition. *T. whipplei* can be transmitted by the fecal–oral route (*7*,*8*). *Campylobacter* spp. are commensals in the gut of a variety of animals, especially poultry; the main infection routes for *Campylobacter* species are foodborne and fecal–oral transmission (*9*). Both *T. whipplei* and *Campylobacter* can be found in sewage (*9*–*11*).

Our study's first limitation was that it was done in real-life settings of diagnostic laboratories where the routine investigations were supplemented by additional PCR tests (Appendix). Pathogens tested and diagnostic techniques differed among the 3 laboratories but were identical within each laboratory between the specimens with and without *T. whipplei*. However, this diversity may even increase the robustness of data. The proportions of fecal samples with no pathogen detected were 81% in Germany, 57% in South Africa, and 29% in Singapore. These findings reflect not only the absence of pathogens but also the pathogen spectrum investigated; a higher number of different pathogens investigated will lead to more positive results, and Singapore had the most comprehensive tests. A high rate of negative findings limits the analyses concerning co-infections of *T. whipplei* with other pathogens.

Second, our study did not include asymptomatic controls, as did the Global Enteric Multicenter Study (*12*,*13*). In South Africa, *T. whipplei* was the most frequent fecal microorganism, followed by *Shigella*, rotavirus, and adenovirus, in descending order, the last

Table 1. Frequency distribution of fecal pathogens in South Africa, Singapore, and Germany*

Location	No. (%)
Centurion, South Africa, 97 specimens	
Tropheryma whipplei	17 (17.53)
Shigella spp.	15 (15.46)
Rotavirus A	7 (7.22)
Adenovirus type F, 40, 41	5 (5.15)
Salmonella spp.	4 (4.12)
Campylobacter spp.	4 (4.12)
Blastocystis hominis	4 (4.12)
Cryptosporidium spp.	4 (4.12)
Giardia lamblia	4 (4.12)
Yersinia enterocolitica	1 (1.03)
Escherichia coli, EPEC, EHEC	1 (1.03)
Aeromonas hydrophila	1 (1.03)
Plesiomonas shigelloides	0
No infective agent detected	55 (56.70)
T. whipplei solo	8 (8.25)
Singapore, 193 specimens	
Rotavirus A	73 (37.82)
Norovirus GG1/2	35 (18.13)
T. whipplei	29 (15.03)
Salmonella spp.	24 (12.44)
Campylobacter spp.	17 (8.81)
A. hydrophila	10 (5.18)
Sapovirus	9 (4.66)
Astrovirus	8 (4.15)
Adenovirus type F, 40, 41	5 (2.59)
G. lamblia	2 (1.04)
Dientamoeba fragilis	2 (1.04)
Shigella spp.	1 (0.52)
B. hominis	1 (0.52)
Vibrio spp.	0
Entamoeba histolytica	0
Y. enterocolitica	0
Cryptosporidium spp.	0
No infective agent detected	55 (28.50)
T. whipplei solo	2 (1.04)
Regensburg, Germany, 300 specimens	
Clostridioides difficile	28 (9.33)
T. whipplei	10 (3.33)
B. hominis	10 (3.33)
Campylobacter spp.	8 (2.66)
G. lamblia	8 (2.66)
Salmonella spp.	3 (1.00)
Y. enterocolitica	2 (0.66)
A. hydrophila	2 (0.66)
Shigella spp.	1 (0.33)
D. fragilis	1 (0.33)
Cryptosporidium spp.	0)
E. histolytica	0
No infective agent detected	242 (80.66)
T. whipplei solo	7 (2.33)

*More than 1 pathogen was detected in some fecal specimens. *T. whipplei* solo indicates that *T. whipplei* was the sole organism detected. EPEC, enteropathogenic *Escherichia coli*; EHEC, enterohemorrhagic *Escherichia coli*.

Table 2. Numbers of enteropathogens in fecal specimens with and without *Tropheryma whipplei* in South Africa, Singapore, and Germany*

Location	Specimens without *T. whipplei*		Specimens with *T. whipplei*	
	No. specimens	No. (rate) of enteropathogens	No. specimens	No. (rate) of enteropathogens
Centurion, South Africa	80	40 (0.50)	17	10 (0.59)
Singapore	164	145 (0.88)	29	38 (1.31)
Regensburg, Germany	290	60 (0.21)	10	3 (0.30)
Total†	534	245 (0.46)	56	51 (0.91)

*Total numbers and rates per specimen of all enteropathogens across all specimens collected at each site; multiple pathogens in a single specimen were counted as multiple entries.
†Incidence rate χ^2, p<0.0001.

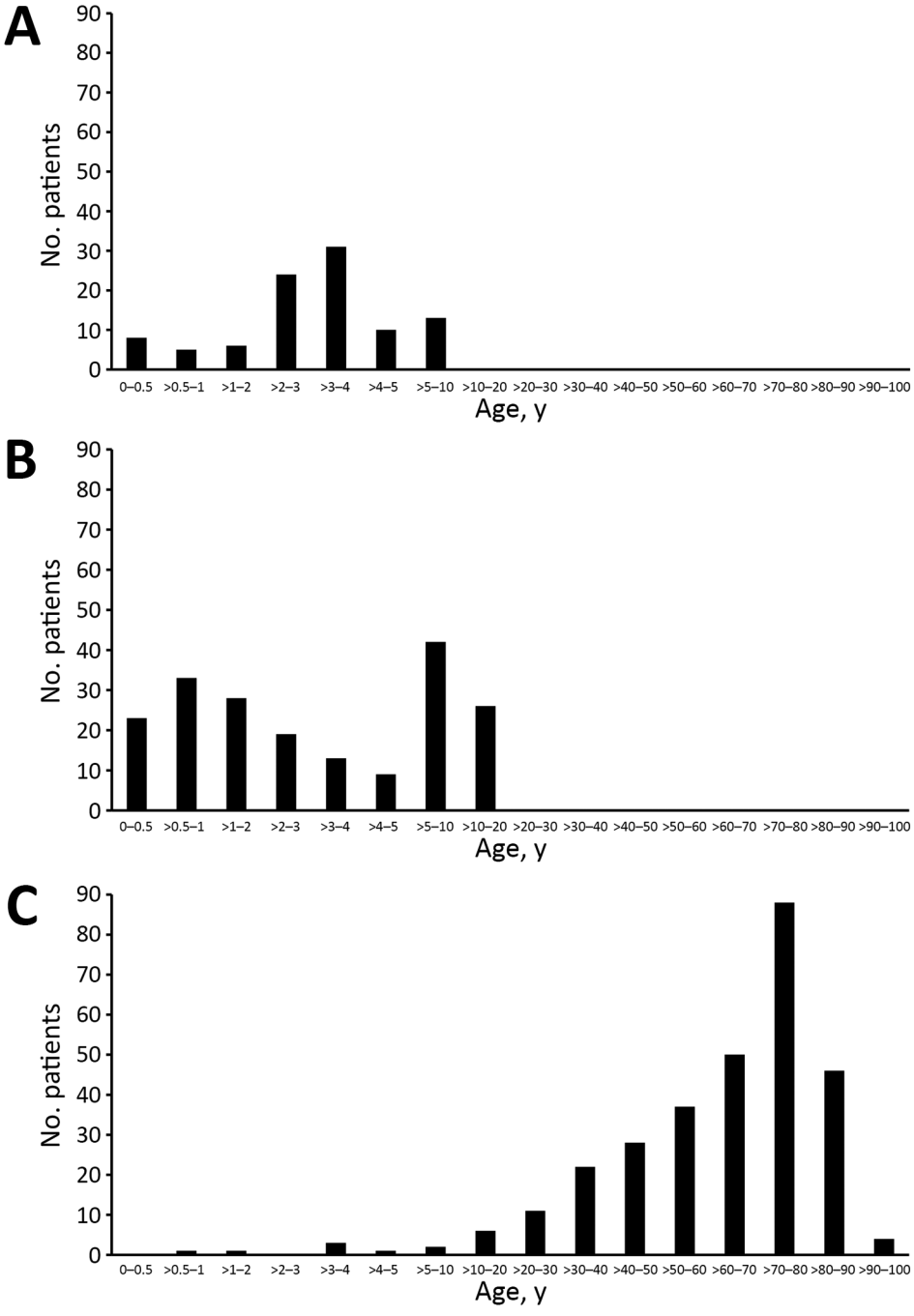

Figure. Age distribution of patients at 3 sites in study of *Tropheryma whipplei* in feces of patients with diarrhea: A) Centurion, South Africa; B) Singapore; and C) Regensburg, Germany.

3 exactly as in the Global Enteric Multicenter Study. In Singapore, *T. whipplei* was third after rotavirus and norovirus, but the ranking of rotavirus may be an artifact because rotavirus antigen was the most frequent ordered laboratory test.

We postulate that the different prevalence of pathogens at the 3 locations (Table 1) is related not just to the different diagnostic strategies but probably also to different climate, development, and hygiene. The Sustainable Development Goals indices for water, sanitation, and hygiene were 68, 66, and 90 in South Africa; 98, 99, and 97 in Singapore; and 100, 100, and 100 in Germany (*14*). These data reflect the order of prevalence of *T. whipplei* in feces in the 3 locations, which is in accordance with a prevalence approaching 50% in children in Laos (*15*).

Conclusions

Using diagnostic specimens from microbiology laboratories on 3 continents, we were able to confirm that *T. whipplei* can be found frequently in the feces of patients with diarrhea (*4*,*5*). Across the 3 locations, the numbers of traditional enteropathogens were significantly increased in specimens also containing *T. whipplei*, and we found an association between the presence of *T. whipplei* and *Campylobacter*. Our findings support the hypothesis that enteric *T. whipplei* may not be causative for diarrhea but may possibly be a result of different sanitary and climatic conditions.

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Appendix

Methods

T. whipplei PCR testing was performed using the LightMix Modular Assay Kit *T. whipplei* (TIB Molbiol, https://www.tib-molbiol.com) (*1*), combined with the extraction control PhHV (TIB Molbiol), using LightCycler 480 instruments (Roche Molecular Diagnostics, https://diagnostics.roche.com), with determination of crossing point (Cp) values in positive samples. Multiplex PCR testing for other pathogens was performed using LightMix Modular Gastroenteritis Panel kits (TIB Molbiol), as reported for *Escherichia coli* (*2*), with varied pathogen composition.

All 3 sites used PCR to test for *T. whipplei*. Testing in Centurion, South Africa, included bacterial culture for *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., *Yersinia enterocolitica*, *Aeromonas hydrophila*, *Plesiomonas shigelloides*, and *Vibrio* spp.; PCR for enteropathogenic *E. coli* (EPEC) and enterohemolytic *E. coli* (EHEC); and parasite microscopy and viral antigen testing (Coris BioConcept, https://www.corisbio.com) for rotavirus and adenovirus F (the latter 2 for children <5 years of age).

Testing in Singapore included routine culture (when requested) for *Salmonella* spp., *Shigella* spp., pathogenic *Campylobacter* spp., *Y. enterocolitica*, and *Vibrio* spp., and antigen testing (when requested) for rotavirus A. Multiplex PCR was done for *Salmonella* spp., *Shigella* spp., pathogenic *Campylobacter* spp., *Y. enterocolitica*, *A. hydrophila*, rotavirus A, adenovirus type F, astrovirus, norovirus genogroups I and II, sapovirus, *Blastocystis hominis*, *Cryptosporidium* spp., *Dientamoeba fragilis*, *Entamoeba histolytica*, and *Giardia lamblia*. Fecal bacterial culture or rotavirus antigen testing was done in subsets of samples based on physician

requests; all fecal specimens were tested by multiplex PCR. Culture for *Y. enterocolitica* was performed for bloody feces, culture for *Vibrio* spp. for watery feces.

Testing in Regensburg, Germany, included PCR for *Salmonella* spp., *Shigella* spp., pathogenic *Campylobacter* spp., *Y. enterocolitica, A. hydrophila, Clostridioides difficile, B. hominis, D. fragilis,* and *G. lamblia*. Because of specific arrangements in Regensburg, fecal samples were anonymized before PCR testing and culture results made unavailable; viral pathogen testing was not done. At all 3 sites, any positive findings were included in the evaluation of the results, regardless of the method by which they were obtained.

All samples that were positive for *T. whipplei* in Centurion and in Regensburg were retested in an independent, previously validated PCR assay targeting the *rpoB* gene of *T. whipplei* (*3*); in Singapore, the nucleic acid extracts were exhausted during prior rounds of testing and were unavailable for retesting.

In an extension of the project, 20 fresh half chickens were purchased at 13 wet markets in Singapore. Skin swabs from each animal were obtained using flocked swabs (FLOQSwabs, https://www.copanusa.com). DNA was extracted from the swabs using the QIAGEN PC purification kit (QIAGEN, https://www.qiagen.com) and subjected to the TIB Molbiol PCRs for *Campylobacter* spp. and *T. whipplei*.

Comparisons between groups on frequency counts (proportions) were done using Fisher exact test, those on incidence rates using a χ^2 test, and those involving age using a 2-sample *t*-test. Statistical significance was set at $p<0.05$.

Results

There were 303 (51.4%) male and 287 (48.6%) female patients in the study. The percentage of males was 60.7% among those with specimens positive for *T. whipplei* and 50.4% among those with specimens negative for *T. whipplei*, but this was not significant (Fisher exact test; $p = 0.16$). The mean age in South Africa was 3.2 years (3.12 and 3.57 years for *T. whipplei*-negative and -positive patients, respectively), in Singapore it was 5.04 years (4.98 and 5.38 years, respectively), and in Germany it was 62.41 years (62.41 and 62.50 years, respectively),

with no significant age differences between *T. whipplei* negative and positive patients within each study site (p = 0.327, 0.674, and 0.989, respectively; 2-sample *t*-test).

Retesting of the nucleic acid extracts from Centurion and from Regensburg with the *rpoB* gene PCR for *T. whipplei* revealed 2 positive TIB Molbiol PCR results for *T. whipplei* with Cp values of 37 and 33.6 in Centurion and 3 positive results with Cp values of 36.8, 36.88, and 39.17 in Regensburg that were not confirmed by the *rpoB* gene PCR. However, even if these specimens were assumed negative, this would not affect the overall results.

The PCR results in swabs of chicken skin in Singapore were positive for *Campylobacter* spp. in 10 of 20 chickens, with Cp values of 35.8 $\pm$ 2.46 (mean ± standard deviation). All test results for *T. whipplei* in chicken skin were negative.

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Appendix Table 1. Numbers of specimens with any enteropathogens in specimens without and with *T. whipplei*

	Specimens without *T. whipplei*		Specimens with *T. whipplei*	
Location	No. specimens	No. (%) of specimens with enteropathogens*	No. specimens	No. (%) of specimens with enteropathogens*
Centurion, South Africa	80	28 (35.0)	17	9 (52.9)
Singapore	164	109 (66.5)	29	27 (93.1)
Regensburg, Germany	290	47 (16.2)	10	3 (30.0)
Total†	534	184 (34.5)	56	39 (69.6)

*Numbers and percentages of specimens that contained any other pathogens, regardless of number of pathogens in a given specimen.
†Fisher exact test, p<0.0001.

Appendix Table 2. Macroscopic and microscopic findings in the fecal specimens without and with *T. whipplei* in Centurion and Singapore

South Africa	Specimens without *T. whipplei* (80 specimens)		Specimens with *T. whipplei* (17 specimens)	
Finding	n	%	n	%
Watery	41	51.3	8	47.1
Erythrocytes	21	26.3	7	41.2
Mucus	32	40.0	8	47.1
Pus cells	60	75.0	12	70.5
Charcot-Leyden crystals	4	5.0	1	5.9
Oil droplets	8	10.0	0	0
Yeast cells	30	37.5	5	29.4
Singapore	**Specimens without *T. whipplei* (164 specimens)**		**Specimens with *T. whipplei* (29 specimens)**	
Finding	n	%	n	%
Watery	24	14.6	2	6.9
Bloody	8	4.9	2	6.9

Appendix Table 3. Frequency of *Campylobacter* spp. and *T. whipplei* detected in the feces of patients with diarrhea

	Samples without *T. whipplei*		Samples with *T. whipplei*	
Location	No. specimens	No. (%) of specimens with *Campylobacter* spp.	No. specimens	No. (%) of specimens with *Campylobacter* spp.
Centurion, South Africa	80	3 (3.8)	17	1 (5.9)
Singapore	164	10 (6.1)	29	7 (24.1)
Regensburg, Germany	290	8 (2.8)	10	0 (0)
Total*	534	21 (3.9)	56	8 (14.3)

* Fisher exact test, p = 0.0035.

Appendix Table 4. Frequency ranking of fecal enteropathogens in specimens without and with *T. whipplei*

Rank		n	%	Rank		n	%
South Africa							
Without *T. whipplei* (80 patients)				With *T. whipplei* (17 patients)			
1	*Shigella* spp.	10	12.5	1	*Shigella* spp.	5	29.4
2	Rotavirus A	5	6.3	2	Rotavirus A	2	11.8
2	Adenovirus type F (41, 42)	5	6.3	2	*Blastocystis*	2	11.8
4	*Salmonella* spp.	4	5	4	*Campylobacter* spp.*	1	5.9
4	*Cryptosporidium*	4	5	5	*Yersinia enterocolitica*	0	0
4	*Giardia lamblia*	4	5	5	*E. coli* EPEC, EHEC†	0	0
7	*Campylobacter* spp.	3	3.8	5	*Cryptosporidium*	0	0
8	*Blastocystis*	2	2.5	5	*Giardia lamblia*	0	0
9	*E. coli* EPEC, EHEC	1	1.3	5	Adenovirus type F (41, 42)	0	0
9	*Aeromonas hydrophila*	1	1.3	5	*Aeromonas hydrophila*	0	0
9	*Yersinia enterocolitica*	1	1.3	5	*Salmonella* spp.	0	0
	No enteropathogen detected	47	58.8		No enteropathogen detected	8	47.1
Singapore							
Without *T. whipplei* (164 patients)				With *Tropheryma whipplei* (29 patients)			
1	Rotavirus A	59	36.0	1	Rotavirus A	14	48.3
2	Norovirus GG1/2	29	17.7	2	*Campylobacter spp.*	7	24.1
3	*Salmonella* spp.	21	12.8	3	Norovirus GG1/2	6	20.7
4	*Aeromonas hydrophila*	10	6.1	4	*Salmonella* spp.	3	10.3
4	*Campylobacter* spp.	10	6.1	4	Sapovirus	3	10.3
6	Sapovirus	6	3.7	6	Astrovirus	2	6.9
6	Astrovirus	6	3.7	7	*Giardia lamblia*	1	3.4
8	Adenovirus type F (41, 42)	5	3.0	7	*Dientamoeba fragilis*	1	3.4
9	*Giardia lamblia*	1	0.6	7	*Blastocystis hominis*	1	3.4
9	*Dientamoeba fragilis*	1	0.6	10	*Cryptosporidium*	0	0
9	*Shigella* spp.	1	0.6	10	Adenovirus type F (41, 42)	0	0
12	*Vibrio* spp.	0	0	10	*Shigella* spp.	0	0
12	*Blastocytis hominis*	0	0	10	*Aeromonas hydrophila*	0	0
12	*Entamoeba histolytica*	0	0	10	*Entamoeba histolytica*	0	0
12	*Yersinia enterocolitica*	0	0	10	*Yersinia enterocolitica*	0	0
12	*Cryptosporidium*	0	0	10	*Vibrio* spp.	0	0
	No enteropathogen detected	52	31.7		No enteropathogen detected	2	6.9
Germany							
Without *T. whipplei* (290 patients)				With *T. whipplei* (10 patients)			
1	*Clostridioides difficile*	26	9.0	1	*Clostridioides difficile*	2	20
2	*Blastocystis hominis*	10	3.5	2	*Giardia lamblia*	1	10
3	*Campylobacter* spp.	8	2.8	3	*Campylobacter* spp.	0	0
4	*Giardia lamblia*	7	2.4	3	*Blastocystis hominis*	0	0

Rank		n	%	Rank		n	%
5	*Salmonella* spp.	3	1.3	3	*Salmonella* spp.	0	0
6	*Aeromonas hydrophila*	2	0.7	3	*Aeromonas hydrophila*	0	0
6	*Yersinia enterocolitica*	2	0.7	3	*Yersinia enterocolitica*	0	0
8	*Shigella* spp.	1	0.3	3	*Shigella* spp.	0	0
8	*Dientamoeba*	1	0.3	3	*Dientamoeba*	0	0
10	*Cryptosporidium*	0	0	3	*Cryptosporidium*	0	0
10	*Entamoeba histolytica*	0	0	3	*Entamoeba histolytica*	0	0
	No enteropathogen detected	235	81.0		No enteropathogen detected	7	70
	Total specimens analyzed	534			Total specimens analyzed	56	
	Total specimens without enteropathogen	334	62.5		Total specimens without enteropathogen	17	30.4
	Total specimens with enteropathogens	200	37.5		Total specimens with enteropathogens	39	69.6

**Campylobacter spp.* is shaded to highlight the changing rank.
†EPEC, enteropathogenic *Escherichia coli*; EHEC, enterohemorrhagic *Escherichia coli*.